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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	15

DATE MAILED: 03/12/98

Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

☐ THE PERIOD FOR RESPONSE:

a) ☐ is extended to run _____ or continues to run _____ from the date of the final rejection

b) ☐ expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition , and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☐ Appellant's Brief is due in accordance with 37 CFR 1.192(a).

☒ Applicant's response to the final rejection, filed 12/12/97 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. ☐ The proposed amendments to the claim and /or specification will not be entered and the final rejection stands because:

   a. ☐ There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.

   b. ☐ They raise new issues that would require further consideration and/or search. (See Note).

   c. ☐ They raise the issue of new matter. (See Note).

   d. ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

   e. ☐ They present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: _____

2. ☐ Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3. ☒ Upon the filing an appeal, the proposed amendment ☒ ~~will not be~~ has been entered ☐ will not be entered and the status of the claims will be as follows:

   Claims allowed: _____
   Claims objected to: _____
   Claims rejected: 1-3, 6, 8-14, 17-22, 26-36

   However;

   ☐ Applicant's response has overcome the following rejection(s): _____

4. ☒ The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection because See examiner's answer

5. ☐ The affidavit or exhibit will not be considered because applicant has not shown good and sufficent reasons why it was not presented.

☐ The proposed drawing correction ☐ has ☐ has not been approved by the examiner.

☐ Other

Bruce C

BRUCE R. C
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PTO-303 (REV. 5-89)

DETAILED ACTION

The amendment and response filed November 12, 2002 has been entered as Paper #25. Claims 17 and 30 have been canceled, claims 1, 2, 8, 12, 13, 18, 26, 27, 29, 31, and 36 have been amended. Claims 37-42 are newly submitted. Currently, claims 1-3, 6, 8-14, 18-21, 26-29, and 31-42 are pending in the application.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in paper #25 would be addressed to the extent that they apply to current rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38 and 40 are rejected under 35 U.S.C. 112 first paragraph, because the specification as originally filed does not describe the invention as now claimed. The original disclosure fails to specify the dose of ionizing radiation as between 50 and 70 Gray as now claimed, thus they are now considered to be new matter.

The original disclosure describes the doses of ionizing radiation as between 5-20Gy such as example VIII, pages 47-48. To the extent that the claimed methods are not described in the instant disclosure, claims 38 and 40 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been properly described.

MPEP 2163.06 notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*" (emphasis added). Applicants are invited to specifically point out the support for the claimed dosing range, or cancel the subject matter in the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 29 and 37 are rejected under 35 U.S.C. 102(e) as being anticipated by *Connelly et al* (US 5,935,935).

Claims are drawn to a pharmaceutical composition comprising a genetic construct comprising a nucleic acid that encodes a TNF-α operatively linked to a constitutive promoter dispersed in a pharmacologically acceptable carrier, wherein the genetic construct is packaged within an adenovirus particle, wherein the adenovirus

particle contains a deletion of the E1 region and/or the E3 region of the adenoviral genome.

Connelly et al teach a genetic construct (DNA sequences) encoding therapeutic agents may be placed into an adenoviral vector, wherein the therapeutic agent is a TNF-alpha (column 11, lines 30-35), wherein the adenoviral vector is packaged as a infectious viral particle (column 10, lines 50-55), wherein the vector is free of at least the majority of adenoviral E1 and E3 region (column 9, lines 23-25). *Connelly et al* further teach that the vector may be administered in combination with a pharmaceutically acceptable carrier suitable for administration to a patient (column 11, lines 6-10). Therefore, *Connelly et al* anticipate the instant claims.

Claims 29 is rejected under 35 U.S.C. 102(e) as being anticipated by *Glorioso et al* (US 6,228,356).

Glorioso et al teach a method of introducing at least one gene encoding a product of interest into cells using recombinant viral vectors including adenovirus (column 11, line 60) encoding and expressing a cytokine, wherein the cytokine is TNF-α (column 12, line 12), wherein the viral particle is introduced to a host in a suitable pharmaceutical carrier (column 24, line 21). Therefore, *Glorioso et al* anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 29 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Zhang et al* (US6,143,290), in view of *Walther et al* (Anticancer Res 1993 Sept;13:1565-74).

Zhang et al teach an adenovirus construct comprising a p53 coding sequence, optionally packaged in virions (abstract and the last paragraph in column 2), and optionally the adenoviral vector lacks a E1 or E3 region (column 4, lines 33-42). *Zhang et al* go on to teach that the p53 expression region is under the control of a strong constitutive promoter such as a CMV promoter or SV40 (column 3, lines 64-66), and is dispersed in a pharmaceutically acceptable solution or buffer (column 5, lines 1-5). *Zhang et al* teach other vectors such as retroviral vectors are known to be used in gene delivery, but "MAJOR PROBLEMS ARE ASSOCIATED WITH USING RETROVIRAL VECTORS FOR GENE THERAPY SINCE THEIR INFECTIVITY DEPENDS ON THE AVAILABILITY OF RETROVIRAL RECEPTORS ON

THE TARGET CELLS, THEY ARE DIFFICULT TO CONCENTRATE AND PURIFY, AND THEY ONLY INTEGRATE EFFICIENTLY INTO REPLICATING CELLS", "THERE REMAINS, THEREFORE, A CLEAR NEED FOR THE DEVELOPMENT OF NEW METHODS FOR INTRODUCING TUMOR SUPPRESSOR GENES, SUCH AS P53, INTO CELLS" (column 2, lines 31-55), *Zhang et al* use a tumor suppressor p53, not TNF-α in the adenoviral vector.

Walther et al teach a vector construct encoding TNF-alpha packaged in a retrovirus particle (paragraph bridging page 1565-66, and 2nd paragraph in left column of 1566). They introduce the recombinant retrovirus into tumor cells causing constitutive expression of TNF-α and reduction of tumor growth (abstract). *Walther et al* teach that compared to the external addition of TNF-α, endogenous expression of TNF-α could use much lower dose yet achieve similar effect, which would reduce the side effect of the anti-tumor agent TNF-α. *Walther et al* do not teach an adenoviral vector.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vectors taught by *Zhang et al or Walther et al*, by simply using an adenoviral vector for expressing TNF-α with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the advantages of adenoviral vectors as taught by *Zhang et al* and the effectiveness in killing tumor cells of TNF-α. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

In paper # 25, applicants argue that Zhang et al reference should not be used for a section 103 rejection because there is an indication that p53 gene expression was rapidly decreased 5 days after the vector administration in the cited patent. The

argument has been fully considered, but found not persuasive. This is because as taught by *Zhang et al* and cited foregoing, every type of vectors has its own advantages and disadvantages. It is within the knowledge of the skilled in the art to determine which vector should be used to express their gene of interest for a particular need. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim Objections

Claim 39 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Claims 29, 37, 38, and 40 are rejected. Claim 39 is objected.

Claims 1-3, 6, 8-14, 18-21, 26-28, 31-36, 41, and 42 are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
April 21, 2003